Claims 16-20, 25 and 27-29 were rejected under 35 U.S.C. §112, first paragraph, as based on a disclosure which is not enabling owing to the lack of the human tau sequence. The rejection of claims 16 and 28 is rendered moot by the cancellation of these claims.

The human tau sequence from Goedert et al. (1989), which was considered critical or essential has been included in a Raw Sequence Listing as "SEQ ID NO: 1" and has been included in the amended specification and is also included in computer readable form on a diskette enclosed herewith. A Declaration by the Applicants' attorney of record has been attached stating that the amendatory material consists of the same material incorporated by reference, and that no new matter has been added. Claims 17, 19, 24, 25 and 27 have been amended to refer to "SEQ ID NO: 1."

In light of the foregoing Amendment, Applicants respectfully submit that the rejection of claims 17-20, 25, 27 and 29 under U.S.C. §112, first paragraph may properly be withdrawn.

The Rejection of Claim 28

Claim 28 stands rejected under 35 U.S.C. §112, first paragraph, as based on a disclosure which is not enabling. The monoclonal antibodies, cTau-7, cTau-8 and cTau-12, have not been deposited because they are antibodies that may be isolated without undue experimentation as guided by the amended disclosure. The subject antibodies were isolated using the standard injection/fusion technique, in mice, as guided by the disclosure (see page 12, line 17- page 13, line10). Should one of

ordinary skill practice the invention by a method guided by the disclosure, he/she would be able to reproducibly obtain the monoclonal antibodies of the invention.

However, in order to expedite prosecution of the application, claims 28 has been cancelled, and thus the rejection of claim 28 is rendered moot by the cancellation of this claim.

The Rejection of Claims 14-20 and 23-30

Claims 14-20 and 23-30 are rejected under 35 U.S.C. §112, first paragraph, because there is not enablement for methods of determining axonal damage using structurally unknown and uncharacterized monoclonal antibodies, or for assaying unknown fragments of a structurally uncharacterized tau protein. The monoclonal antibodies, cTau-7, cTau-8 and cTau-12, have not been deposited because they are known antibodies that can be isolated from nature without undue experimentation. The antibodies were isolated using the standard injection/fusion technique, in mice, as guided by the disclosure (see page 12, line 17-page 13, line 10).

The rejection of claims 16 and 28 is rendered moot by the cancellation of these claims.

Applicants respectfully submit that one of ordinary skill in the art should be able to practice the invention guided by the present disclosure, so as to reliably obtain the monoclonal antibodies to the tau protein structures disclosed, and use them in the practice of the method of the present invention.

Applicants have also amended claim 14 to specify that antibodies are raised against an axonally-derived protein selected from the group consisting of isoforms of tau protein of SEQ ID NO: 1 and derivatives and fragments thereof, thus providing structural guidance as to the monoclonal antibodies to be used in the method of the present invention.

Accordingly, in light of the foregoing Amendment, Applicants respectfully submit that the rejection of claims 14, 15 17 – 20 and 23 – 27, 29 and 30 under 35 U.S.C. §112, first paragraph, may now properly be withdrawn.

The Rejection under 35 U.S.C. Section 112, Second Paragraph

Claims 19-20 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended the specification to include the peptide sequence of tau protein, and have amended claim 19 (from which claim 20 depends) to recite SEQ ID NO: 1.

Applicants respectfully submit that this grounds for rejection has been overcome by the recitation of "SEQ ID NO: 1" in amended claim 19 and proper submission of a Raw Sequence Listing, and that this rejection may now be properly withdrawn.

Claim Rejections under 35 U.S.C. §102

Claims 14-20, 23-27 and 29-30 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Vandermeeren et al. (WO 94/13795).

In order for a prior art reference to anticipate an invention, every element of the claimed invention must be identically shown in the reference and there must be no difference between the claimed invention and the reference, as viewed by a person of ordinary skill in the art.

Vandermeeren et al. is teaching a method of detection of or diagnosis of filamentous tau inclusion bodies in patients with tauopathies (group of neurodegenerative brain diseases characterized by prominent filamentous tau inclusion bodies). Vandermeeren et al. (WO 94/13795, pg. 3) describe their invention as "[aiming] at providing a process for the detection or diagnosis *in vitro* of brain diseases involving tau protein." This group of brain diseases that involve tau proteins are referred to as tauopathies (Goedert, Prog. Br. Res. 1998). Tauopathies are a group of neurodegenerative diseases characterized by prominent filamentous tau inclusion bodies in brain (Lee and Trojanowski, 1999). Vandermeeren et al (WO 94/13795, pg. 9) indicate that "the antigen of the invention is advantageously contained in the brain, in the cerebrospinal fluid or the serum of a patient having Alzheimer's disease, Down's syndrome, Pick's disease, subacute sclerosing panencehalitis (SSPE) or other neurologic diseases in which normal tau or abnormally phosphorylated tau are implicated". All of the specifically named diseases are tauopathies characterized by tau

inclusion bodies (Goedert 1998, Table 1). The reference to other neurologic diseases in which tau is implicated refers to the numerous other tauopathies which are characterized by tau inclusion bodies, e.g. progressive supernuclear palsy, etc.

Vandermeeren et al (WO 94/13795) thus relates only to a method for detecting the filamentous tau inclusion bodies characteristic of tauopathies. Vandermeeren et al. prepared tissue sections from Alzheimer's brain and normal brain and demonstrated that the monoclonal antibodies, which are the subject of their invention, labeled tau inclusion bodies in Alzheimer's brain (WO 94/13795, pg. 18, Figure 2A and 2B). As would be expected, these tau inclusion bodies greatly increase the levels of tau in the brain of tauopathy patients (Khatoon et al, 1992). Vandermeeren et al (WO 94/13795, pg. 3) reference this fact stating that "in Alzheimer's-affected brain sections, tau levels were eight-fold higher as compared with levels in normal brain homogenates". Vandermeeren et al. disclose that these increased levels of tau associated with tau inclusion bodies are also present in CSF and serum, stating that "the antigen of the invention is advantageously contained in the brain, in the cerebrospinal fluid or the serum of a patient having Alzheimer's disease, Down's syndrome, Pick's disease, subacute sclerosing panencehalitis (SSPE) or other neurologic diseases in which normal tau or abnormally phosphorylated tau are implicated". All of these diseases are tauopathies characterized by tau inclusion bodies (Lee and Trojanowski, 1999).

In contrast, the method of the present invention is directed to a method of determining axonal damage in the human central nervous system, instead of a method

of detecting tau inclusion bodies in patients with tauopathies taught by Vandermeeren et al. Accordingly, Applicants respectfully submit that the Vandermeeren et al. reference does not anticipate the present invention which claims a method of detecting axonal damage.

Conclusion

In view of the foregoing Amendment and accompanying Remarks, Applicants respectfully submit that the subject application is in condition for allowance and should be passed to issuance upon payment of the appropriate fees. Further favorable action is respectfully solicited, and telephone inquiry to the undersigned attorney to clarify or otherwise expedite prosecution of the subject application is encouraged.

Respectfully submitted,

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Dated: May 22, 2000 By: _____

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#15

Serial No.:	09/035,708	
Group Art Unit:	1644	
Filing Date:	March 5, 1999	**DECLARATION**
Examiner:	Robert C. Hayes, PhD.	
Inventor:	Zemlan, et al.	
Title:	METHOD OF DETECTING AXONAL DAMAGE, ASSOCIATED DISEASE STATES AND RELATED MONOCLONAL ANTIBODIES AND PROTEIN CONTROLS THERFOR	

DECLARATION

As below named practitioner for the Applicant for which a patent is sought on the invention entitled METHOD OF DETECTING AXONAL DAMAGE, ASSOCIATED DISEASE STATES, AND RELATED MONOCLONAL ANTIBODIES AND PROTEIN CONTROLS THEREFOR, I hereby state that the amendatory material, incorporating the peptide sequence identified in the subject application as Seq. I.D. No.1 is the same peptide sequence contained in the reference by Goedert et al. (1989) that had been incorporated by reference in the subject application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

Full name of practitioner Roger A. Gilcrest, Reg. No. 31,954

Date May 22, 2000